

TRANSMITTAL LETTER TO THE UNITED STATES
DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. 371

NHC202119-US

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR

To Be Assigned 10/089599

INTERNATIONAL APPLICATION NO.

PCT/GB00/03729

INTERNATIONAL FILING DATE

September 29, 2000

PRIORITY DATE CLAIMED

October 1, 1999

TITLE OF INVENTION

Anti-Inflammatory Pharmaceutical Formulations

APPLICANT(S) FOR DO/EO/US

Woolfe, Austen, John

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (24) indicated below.
4. ☐ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
 - a. ☐ is attached hereto (required only if not communicated by the International Bureau).
 - b. ☒ has been communicated by the International Bureau.
 - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
 - a. ☐ is attached hereto.
 - b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
 - a. ☐ are attached hereto (required only if not communicated by the International Bureau).
 - b. ☐ have been communicated by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☐ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☐ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☐ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☒ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

Copy of the published application for PCT/GB00/03729

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR 1.101) 10/0009599	U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR 1.101) PCT/GB00/03729	ATTORNEY'S DOCKET NUMBER NHC202119-US
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24. The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

<input type="checkbox"/> Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO	\$1000.00
<input checked="" type="checkbox"/> International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO	\$860.00
<input type="checkbox"/> International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO	\$710.00
<input type="checkbox"/> International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4)	\$690.00
<input type="checkbox"/> International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4)	\$100.00

ENTER APPROPRIATE BASIC FEE AMOUNT =

Surcharge of \$130.00 for furnishing the oath or declaration later than months from the earliest claimed priority date (37 CFR 1.492 (e)).	<input type="checkbox"/> 20 <input checked="" type="checkbox"/> 30
	\$130.00

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	FEE	TOTAL
Total claims	15 - 20 =	0	x \$18.00		\$0.00
Independent claims	1 - 3 =	0	x \$80.00		\$0.00
Multiple Dependent Claims (check if applicable). <input type="checkbox"/>					\$0.00
TOTAL OF ABOVE CALCULATIONS =					\$990.00
<input type="checkbox"/> Applicant claims small entity status. (See 37 CFR 1.27). The fees indicated above are reduced by 1/2.					\$0.00
SUBTOTAL =					\$990.00
Processing fee of \$130.00 for furnishing the English translation later than months from the earliest claimed priority date (37 CFR 1.492 (f)).					\$0.00
TOTAL NATIONAL FEE =					\$990.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) (check if applicable). <input type="checkbox"/>					\$0.00
TOTAL FEES ENCLOSED =					\$990.00
					Amount to be refunded \$
					charged \$

CALCULATIONS PTO USE ONLY

a. ☐ A check in the amount of _____ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. **50-0943** in the amount of **\$990.00** to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **50-0943** A duplicate copy of this sheet is enclosed.


d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

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43,750
 REGISTRATION NUMBER

March 29, 2002
 DATE

ANTI-INFLAMMATORY PHARMACEUTICAL FORMULATIONS

This invention relates to pharmaceutical formulations of anti-inflammatory drugs, particularly non-steroidal anti-inflammatory drugs (NSAIDs).

These NSAIDs are used for the treatment of inflammatory conditions such as osteoarthritis or rheumatoid arthritis. A side effect of the oral administration of NSAIDs particularly with long term usage, is a liability to ulcerogenic effects. NSAID induced ulcers in the stomach are potentially dangerous because few or no symptoms may be detected until significant damage has been caused. Certain prostaglandins, for example misoprostol have been shown to reduce and even prevent such ulcers.

Various patent applications relate to use of misoprostol with immediate release drugs, for example GB-A-2135881 (Farmitalia Carlo Erba), WO91/16896 (G D Searle), or where a gastric resistant coating is put over the NSAID in an attempt to reduce further gastric erosion due to release in the stomach of the NSAID, for example WO91/16895, WO91/16886 (G D Searle).

There is an increasing use of sustained release preparations of NSAID drugs to reduce the number of doses required by the patient each day. Although the theory of such preparations is that the majority of the drug is released in the intestine rather than the stomach, in practice there is a significant occurrence of gastric problems. This may be due to release of small amounts of drug within the stomach.

The incorporation of misoprostol into such products to reduce the potential for such problems has not previously been disclosed.

According to the present invention an oral pharmaceutical dosage form includes a mixture of a delay release formulation of a NSAID and a mixture containing one or more excipients and a prostaglandin, wherein the delay release NSAID formulation preferably comprises coated granules.

The prostaglandin mixture may be provided in the form of a powder which is mixed with the NSAID formulation within the dosage form.

The dosage form may comprise a tablet, capsule, granule or other commonly used configuration. However preferred dosage forms comprise a capsule containing multi-particulate granules of the NSAID formulation together with the powdered prostaglandin mixture. The NSAID granules preferably have coatings adapted to provide programmed release according to the position in the gastrointestinal tract. Use of such coated granules provides a more repeatable release along the gastrointestinal tract and may reduce gastric erosion because the small pellets or granules are easily moved and do not adhere readily to the folds of the gastric wall.

Granules for use in accordance with this invention may have a single slowly erodible coat or may comprise mixtures of granules with differing levels or types of coating adapted to provide a continuous or distributed release profile through the gastrointestinal tract. The delay afforded may range from a minimal delay to several hours, dependent on the pH of the gastrointestinal tract in the immediate vicinity.

The NSAID is preferably but not exclusively one of reasonably low weight per standard dose, that is 200 mg or below. Examples of suitable NSAIDs include tiaprofenic acid, piroxicam, flubiprofen, tenoxicam, meloxicam or similar molecules. Salts or other derivatives of these

drugs may be employed in a conventional manner. Most preferably the drug is diclofenac sodium, ketoprofen or indomethacin. Mixtures may be used.

Drug delivery using capsules avoids a further compression step as may be necessary during tablet manufacture.

Granules, for example composed of diclofenac sodium and a methyl methacrylate (eg Eudragit L 30 D-55) may be prepared by blending the ingredients in a planetary mixer with slow addition of water to produce granules. In a preferred process very fine granules are produced to avoid a need for milling before compaction into tablets or incorporation into capsules. Use of granules with the dimension of 200 - 1000 μm , preferably 300 to 500 μm is particularly suitable. Tablets may be produced by coating these granules with a barrier coating material for example a cellulosic material such as hydroxypropylmethyl cellulose or hydroxypropyl cellulose. Tablets may be produced by coating these granules.

An alternative method of forming coated granules is by spraying a solution of Eudragit onto a bed of diclofenac sodium or other drug and any necessary excipients for example using a fluid bed coating apparatus. The process is preferably controlled to produce fine granules which do not require milling before incorporation into tablets or capsules.

The coating for the granules may include cellulose derivatives eg hydroxypropyl methyl cellulose, methacrylic acid and derivatives eg methyl methacrylates for example, Eudragit® (Rhom Pharm), especially Eudragit L or S. Other standard enteric coating materials may be used for example phthalates, eg cellulose acetate phthalate or preferably hydroxypropylacetate phthalate or polyvinylacetate

phthalate. Mixtures of these and other materials may be used to produce delay release coated beads. Normally the coating will include plasticisers eg polyethylene glycol, triacetin or phthalate esters.

The prostaglandin component preferably contains misoprostol optionally together with one or more inert excipients. The prostaglandin is normally provided as a 1:10 or 1:100 dilution on an inert cellulose or other binder or filler. Especially useful material for this invention is hydroxypropyl methyl cellulose. The dosage of prostaglandin may be chosen to be suitable to prevent or reduce stomach ulceration caused by the NSAID. A suitable dose of misoprostol is between 10 - 50 μ g preferably 50 - 200 μ g per dosage form but this may be increased or decreased depending on the NSAID used.

Preferred dosage forms comprise capsules, preferably hard gelatin capsules.

Tablets where the prostaglandin is mixed with one or more binding agents may be bi-layer tablets wherein the NSAID is formed into a first layer and the prostaglandin is then compressed onto it. A tri-layer tablet with an inert intermediate barrier layer between the NSAID and prostaglandin layers may be employed.

In preferred embodiments of the invention, the potential for gastric erosion is reduced by ensuring that the prostaglandin is released before the NSAID. Any beads for immediate or rapid release are coated with an inert coating which defer solubility in gastric fluid, for example for a period of 30 minutes. Such materials include cellulose derivatives for example hydroxypropyl methyl cellulose, methyl or ethyl celluloses or other sealants eg Zein. Thin coatings of methacrylate derivatives eg polyhydroxymethacrylate or other materials such as hardened

gelatine, waxes, starches or polyvinyl pyrrolidone may be used. Other portions of the granules may be coated with methacrylate derivatives, phthalate, for example hydroxypropyl methyl cellulose phthalate or similar materials to give an appropriate release profile as is well known in the art.

The invention is further described by means of example, but not in any limitative sense.

Example 1

The following formulation was mixed with water in a planetary mixer to make enteric coated granules:

diclofenac sodium	96.2%
Eudragit L 30 D-55	3.8%

The granules were dried and compacted into layered tablets having the following composition:

diclofenac-containing granules	26.0%
microcrystalline cellulose	73.5%
magnesium stearate	0.5%

The tablets were compared to a proprietary diclofenac-containing tablet available under the trade mark Arthrotec. Bioequivalence studies showed the release of diclofenac to be essentially similar.

Granules containing 35% diclofenac sodium ie 75 mg drug per dose were prepared.

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EXAMPLE 2

A two layer tablet was made as follows:

The following ingredients were mixed together:

Diclofenac sodium	75.95%
Eudragit 130-d55 (30% solid dispersion)	12.66%
Lactose (20 mesh)	11.4%
Water	

The mixture was blended, dried and milled to give diclofenac-containing granules. The granules (25%) were mixed with microcrystalline cellulose (Avicel pH 200 and pH 112) to give a total of 69%. Dry Eudragit 1100 powder (5%) and hydrogenated castor oil (1%) were added. The mixture was pressed into half tablets with a tablet weight of 400 mg.

A misoprostol layer was formed as follows:

A misoprostol dispersion (1:100) 6.7% was combined with microcrystalline cellulose (Avicel pH 112) 88.33%, croscarmellose sodium (4%) and hydrogenated castor oil to give a tablet weight of 300 mg. The combined bi-layered tablet had a total weight of 700 mg.

Dissolution properties were determined by exposure to acid medium for two hours followed by measurement of dissolution in alkaline buffer. The following results were obtained.

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SOLUBILITY/%		
Time in alkaline buffer	Example 2 tablets	Arthrotec tablets
30 sec	1.6 - 5.0	0 - 0.5
5 min	11 - 13	1.3 - 3.1
30 min	51 - 60	61 - 71
60 min	86 - 90	74 - 96

CLAIMS

1. An oral pharmaceutical dosage form including a mixture of a delay release formulation of a non-steroidal anti-inflammatory drug (NSAID) and a mixture containing a prostaglandin and one or more excipients; wherein the NSAID formulation comprises coated granules.
2. A dosage form as claimed in claim 1, wherein the granules have a dimension of 200 - 1000 μm .
3. A dosage form as claimed in claim 2, wherein the granules have a dimension of 300 - 500 μm .
4. A dosage form as claimed in any preceding claim, wherein the prostaglandin is misoprostol.
5. A dosage form as claimed in any preceding claim, wherein the mixture is a powder comprising prostaglandin absorbed on an inert substance.
6. A dosage form as claimed in any preceding claim, comprising a capsule containing multi-particulate granules of the NSAID formulation together with the powdered prostoglandin mixture.
7. A dosage form as claimed in any preceding claim, comprising a mixture of granules with different levels or types of coating.
8. A dosage form as claimed in any preceding claim, wherein the NSAID is selected from the group consisting of

tiaprofenic acid, piroxicam, flubiprofen, tenoxicam, meloxicam and salts and derivatives thereof.

9. A dosage form as claimed in claim 8, wherein the NSAID is selected from the group consisting of diclofenac sodium, ketoprofen and indomethacin and mixtures thereof.

10. A dosage form as claimed in any of claims 1 to 9, wherein the dosage of misoprostol is 50 to 200 μ g per dosage form.

11. A dosage form as claimed in any preceding claim, wherein the granules have a coating of one or more compounds selected from the group consisting of: hydroxypropyl methyl cellulose, methacrylic acid and derivatives, methyl methacrylates, cellulose acetate phthalate, hydroxypropylacetate phthalate, polyvinylacetate phthalate and mixtures thereof.

12. A dosage form as claimed in claim 11, wherein the coating includes a plasticiser selected from the group consisting of: polyethylene glycol, triethyl acetate or phthalate esters.

13. A dosage form comprising a filled hard gelatin capsule containing a dosage form as claimed in any preceding claim.

14. A dosage form as claimed in any of claims 1 to 12, comprising a bi-layer or tri-layer tablet.

15. A dosage form as claimed in claim 14, wherein granules of the NSAID are coated with a coating selected

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from the group consisting of: hydroxypropyl methyl cellulose, methacrylic acid and derivatives, methyl methacrylates, cellulose acetate phthalate, hydroxypropylacetate phthalate, polyvinylacetate phthalate and mixtures thereof are compressed into a first layer and a second layer comprising the prostaglandin and excipients is compressed onto the first layer.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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- (74) Agent: **BROWNE, Robin, Forsythe; Urquhart-Dykes & Lord**, Tower House, Merrion Way, Leeds LS2 8PA (GB).
- (21) International Application Number: **PCT/GB00/03729**
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- (30) Priority Data:
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- (71) Applicant (*for all designated States except US*): **NORTON HEALTHCARE LTD.** [GB/GB]; Albert Basin, Royal Docks, London EC16 2QJ (GB).
- Published:**
— *With international search report.*
— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*
- (72) Inventor; and
- (75) Inventor/Applicant (*for US only*): **WOOLFE, Austen, John** [GB/GB]; 31 Emberson Way, North Weald, Essex CM19 6DL (GB).
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

**WO 01/24778 A1**(54) Title: **ANTI-INFLAMMATORY PHARMACEUTICAL FORMULATIONS**

(57) Abstract: An oral pharmaceutical dosage form including a mixture of a delay release formulation of a non-steroidal anti-inflammatory drug (NSAID) and a mixture containing a prostaglandin and one or more excipients.

NHC202119US

DECLARATION AND POWER OF ATTORNEY
(Attorney Docket No. NHC202119US)

As below-named inventor, I hereby declare that:

My residences, post office addresses and citizenship are as stated below next to my name.

I believe I am the original, first and only inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled:

ANTI-INFLAMMATORY PHARMACEUTICAL FORMULATIONS

the specification of which (check only one):

- ☐ is attached hereto.
- ☒ was filed as United States Patent Application
Serial No. 10/089,599
on March 29, 2002
and was amended
on _____
(if applicable)
- ☐ was filed as PCT Patent Application
Serial No. _____
on _____
and was amended under PCT Article 19
on _____
(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability of the claims of this application in accordance with Title 37, Code of Federal Regulations, Sections 1.56(a) and 1.56(b).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

NHC202119US

**PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS
UNDER 35 U.S.C. §119:**

COUNTRY (if PCT indicate PCT)	APPLICATION NUMBER	DATE OF FILING	PRIORITY CLAIMED UNDER 35 U.S.C. §119 (YES/NO)
GB	9923139.1	1 October 1999	Yes
GB	0000483.8	11 January 2000	Yes

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional patent application(s) listed below:

APPLICATION NUMBER	DATE OF FILING	STATUS: (PENDING OR ABANDONED)
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I hereby claim the benefit under Title 35, United States code, § 120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, § 1.56 which occurred between the filing date of the prior applications and the national or PCT international filing date of this application:

**PRIOR U.S. APPLICATION OR PCT INTERNATIONAL APPLICATION(S)
DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. § 120:**

APPLICATION NUMBER	DATE OF FILING (day, month, year)	STATUS: (PATENTED, PENDING OR ABANDONED)
PCT/GB00/03729	29 September 2000	Abandoned

POWER OF ATTORNEY: As named inventor, I hereby appoint the following attorneys and/or agents to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

Simona A. Levi-Minzi, Ph.D.

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NHC202119US

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Wherefore, I petition that letters patent be granted to me for the invention or discovery described and claimed in the attached specification and claims, and hereby subscribe my name to said specification and claims and to the foregoing declaration, power of attorney, and this petition.

I hereby declare that all statements made herein of our my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18, of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

100 Full name of sole inventor: Austen John Woolfe

Inventor's signature

A. J. Woolfe

Date

7/06/2002

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